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A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife

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ABSTRACT

Background: This longitudinal study assesses characteristics associated with adolescents' nonmedical use of prescription opioids (NMUPO) including: frequency, co-ingestion, motives, specific opioid type; sequence of initiation of medical use of prescription opioids and NMUPO in relationship to subsequent substance use disorder (SUD) symptoms.

Methods: Twenty-one independent national cohorts of U.S. high school seniors (n = 8,373) were surveyed and followed 17 years from adolescence to age 35.

Results: The majority of adolescents who engaged in NMUPO reported occasional/frequent NMUPO, non-pain relief motives for NMUPO, simultaneous co-ingestion involving NMUPO and other drugs, opioid analgesics with high misuse potential, and multiple types of opioid analgesics. Adolescents who reported NMUPO for pain relief, NMUPO involving opioid analgesics with high misuse potential, or multiple prescription opioids had significantly greater odds of SUD symptoms at age 35, relative to those who had no history of NMUPO during adolescence. In addition, medical use of prescription opioids after initiating NMUPO (or NMUPO only) during adolescence was associated with significantly greater odds of subsequent SUD symptoms at age 35 relative to those who reported the medical use of prescription opioids only or had no medical use or NMUPO during adolescence.

Conclusions: This is the first U.S. national prospective study to examine the relationships between adolescents' NMUPO characteristics and later SUD symptoms in early midlife. Several characteristics (frequency, co-ingestion, motives, opioid type, and medical/NMUPO initiation history) were identified that could be used to screen and detect high-risk youth for indicated interventions to reduce prescription opioid misuse and SUDs.

1. Introduction

Prescription opioid misuse and opioid use disorder represent a worldwide problem (GBD 2016 Alcohol and Drug Use Collaborators, in press; Giraudon et al., 2013; Manchikanti et al., 2010). There was a significant increase in opioid analgesic prescribing in the U.S. and worldwide over the past three decades followed by recent signs of a decline (Atluri et al., 2014; Bohnert et al., 2018; Dart et al., 2015; Fortuna et al., 2010; Gilson et al., 2004; Hastie et al., 2014; Joranson et al., 2000; Manchikanti et al., 2010; McCabe et al., 2017; Novak et al., 2004; Sandvik et al., 2016; Wagemaakers et al., 2017; Weisberg et al., 2014; Zacny et al., 2003). Opioid analgesic prescribing trends raised concerns regarding the changes in availability of prescription opioids contributing to nonmedical use of prescription opioids (NMUPO) and

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adverse consequences such as substance use disorders (SUDs) and overdoses (Bohnert et al., 2011; Centers for Disease Control and Prevention, 2012; Crane, 2015; Edlund et al., 2015; Han et al., 2015; McCabe et al., 2013, 2016; Miech et al., 2015; Substance Abuse and Mental Health Services Administration, 2013). There are some age groups that appear are more vulnerable than others to opioid-related adverse consequences. The number of U.S. NMUPO-related emergency department visits among those aged 18–34 years increased over 200 percent in recent years, an increase greater than any other age group (Crane, 2015).

Despite the public health concerns regarding opioid-related consequences, there remains a paucity of prospective longitudinal research that examines characteristics associated with NMUPO (e.g., frequency, motives, co-ingestion, and medical/NMUPO initiation) during adolescence and their relationship with later substance-related problems in adulthood (Compton and Volkow, 2006a, 2006b; Nargiso et al., 2015; Young et al., 2012a). To date, existing evidence is based primarily on cross-sectional or regional studies and indicates that higher frequency of NMUPO, non-pain relief motives for NMUPO, and co-ingestion of NMUPO with other drugs are associated with increased risk of substance use behaviors during adolescence (Boyd et al., 2006; Catalano et al., 2011; Han et al., 2015; McCabe et al., 2006, 2007a, 2007b). Furthermore, most studies combine prescription opioids without distinguishing between prescription opioids with a wide range of misuse potential (e.g., Schedule II vs. Schedule III/IV/V) or the number of prescription opioids used nonmedically. To date, no prior research has examined the long-term relationships between these key characteristics of NMUPO in adolescence and subsequent SUD symptoms during adulthood.

Although prior regional and national U.S. studies indicate most adolescents use opioid medications appropriately, medical use of prescription opioids during adolescence is associated with greater odds of subsequent prescription opioid misuse (Harbaugh et al., 2018; McCabe et al., 2013, 2016; Miech et al., 2015). Furthermore, adolescents who reported a history of both medical use of prescription opioids and NMUPO have increased odds of subsequent SUD symptoms (McCabe et al., 2016). The increased risk among medical users with a history of NMUPO suggests a more in-depth examination is warranted to identify the sequence of initiation of medical use of prescription opioids and NMUPO that are associated with subsequent SUDs.

The main objectives of this study were to assess the relationships among adolescents' NMUPO characteristics (e.g., frequency, motives, misuse potential, co-ingestion, and medical prescription opioid use history) and subsequent SUD symptoms at age 35. Using U.S. national panel data, we examined the associations among NMUPO frequency, NMUPO motives, NMUPO co-ingestion, NMUPO count/drug schedule, and initiation of medical prescription opioid use and NMUPO during adolescence in relation to age 35 SUD symptoms.

2. Methods

Our study used national U.S. panel data from the Monitoring the Future (MTF) study (Schulenberg et al., 2018). Based on a three-stage sampling procedure, MTF surveyed nationally representative samples of approximately 17,000 U.S. high school seniors each year since 1975 using questionnaires administered in classrooms. Stage 1 was the selection of geographic areas; stage 2 was the selection of schools; and stage 3 was the selection of students within each school. Approximately 2450 high school seniors were randomly selected each year for biennial follow-ups and surveyed using mailed questionnaires through age 30. They were also followed up at age 35. Our study used data from high school seniors who were randomly assigned to complete questionnaire Form 1 at baseline (one of six questionnaires provided at baseline) and the single form provided to all panel respondents at age 35. Baseline Form 1 contained information regarding both medical use of prescription opioids and NMUPO. The MTF age 35 survey includes questions concerning adult SUD symptoms including symptoms of alcohol use disorder (AUD), cannabis use disorder (CUD), and other drug use disorder (ODUD).

Our study used data from 21 cohorts of high school seniors (surveyed in 1976 through 1996) who were followed up at age 35 (surveyed in 1993 through 2013). The student response rates at baseline over the study period ranged from 77% to 86%. Most non-response was due to the respondent being absent (less than 1.5% refused to participate). The MTF panel oversamples drug users from the 12th-grade sample to secure a population of drug users to follow into adulthood (appropriate weights are then used to best approximate population estimates in the follow-up). The overall weighted retention rate for the longitudinal sample from baseline (12th-grade) to age 35 was 54%. To help correct for potential attrition bias consistent with recent MTF panel analyses (McCabe et al., 2016; Merline et al., 2008; Schulenberg et al., 2016), we incorporated attrition weights to account for respondent characteristics associated with non-response at follow up. The MTF project design and sampling methods are described in greater detail elsewhere (Bachman et al., 2015; Miech et al., 2018; Schulenberg et al., 2018).

2.1. Sample

As illustrated in Table 1, the weighted longitudinal sample included 8373 individuals (52.9% female and 47.1% male). The racial/ethnic distribution of the sample was 73.5% White, 11.9% Black, 6.4% Hispanic, and 8.1% from other racial/ethnic categories. Attrition analyses compared those in the longitudinal sample who participated at both waves with those who participated at baseline only. Results showed that retention was *not* significantly different for baseline frequency of lifetime NMUPO, frequency of past-year NMUPO, motives for NMUPO, and co-ingestion of NMUPO and other substances. There were statistically significant associations between retention and sex (higher for females), race/ethnicity (higher for Whites), geographical region (higher for Midwest), and cohort year (higher for earlier cohorts). The use of attrition weights helped correct for these biases in the analytic sample.

Table 1
Descriptive statistics for the longitudinal sample at baseline (age 18).

Baseline characteristics at age 18	Weighted study sample % (n = 8373)
Sex	
Male	47.1
Female	52.9
Race/Ethnicity	
White	73.5
Black	11.9
Hispanic	6.4
Other race/ethnicity	8.1
Parental Education	
At least one parent has a college degree or higher	40.0
Neither parent has a college degree	60.0
Region	
Northeast	21.3
Midwest	27.3
South	33.9
West	17.5
Urbanicity	
Large metropolitan statistical area	23.4
Other metropolitan statistical area	46.4
Non-metropolitan statistical area	30.2
12th Grade Cohort Year	
1976-1980	23.0
1981-1985	24.2
1986-1990	25.0
1991-1996	27.8

Note: Prevalence estimates based on weighted data.

2.2. Measures

The MTF study was designed to assess a wide range of behaviors, attitudes, and motives. For the present study, we selected specific baseline measures for analysis based on prior work examining correlates associated with medical use of prescription opioids and NMUPO, including demographic characteristics: sex, race/ethnicity, U.S. Census geographic region, urbanicity based on metropolitan statistical area, parental education, and annual alcohol, marijuana, and other drug use.

Medical use of prescription opioids at baseline (age 18) was assessed by asking whether respondents had ever taken prescription opioids because a doctor told them to use the medication. Respondents were informed that prescription opioids are prescribed by doctors and that drug stores and are not supposed to sell them without a prescription. Respondents were provided a list of several examples of prescription opioids (e.g., codeine, methadone). The response options included: (1) No; (2) Yes, but I had already tried them on my own; and (3) Yes, and it was the first time I took any.

Nonmedical use of prescription opioids at baseline (age 18) was based on two separate questions measuring lifetime and past-year NMUPO (i.e., "taken any narcotics other than heroin on your own—that is, without a doctor telling you to take them?"). Respondents were also provided a list of several examples of prescription opioids. The response scales for these two questions ranged from (1) No occasions to (7) 40 or more occasions. Respondents who reported past-year NMUPO were asked to indicate the specific prescription opioids they used in the past-year without a doctor's orders. For purposes of the present study, these prescription opioids were categorized into Controlled Substances Act Schedule II (e.g., methadone, Demerol, morphine, opium, laudanum) and Schedule III, IV, and V (e.g., codeine, talwin, paregoric, other).

Based on the medical and nonmedical use questions, a variable with five mutually exclusive categories of lifetime use of prescription opioids at baseline (age 18) was developed: (1) No medical or nonmedical use; (2) Medical use only; (3) Medical before nonmedical use; (4) Nonmedical before medical use; and (5) Nonmedical use only.

Co-ingestion of NMUPO and other drugs at baseline (age 18) was measured with ten separate items focused on whether prescription opioids were nonmedically used at the same time as other drugs so that the effects overlapped for the following drugs: Alcohol, marijuana, LSD, hallucinogens other than LSD, amphetamines, sedatives, barbiturates, tranquilizers, cocaine, and heroin. The response scale for each item ranged from (1) Not at all to (5) Every time. A binary variable was constructed based on the 10-items to determine whether any simultaneous co-ingestion of prescription opioids and other drugs occurred in the past-year at baseline: (1) Any past-year simultaneous co-ingestion of prescription opioids and other drugs, and (2) No past-year simultaneous co-ingestion of prescription opioids and other drugs.

Motives for NMUPO at baseline (age 18) were assessed by asking respondents who reported NMUPO to indicate the most important reasons for NMUPO (mark all that apply). The list of motives included, but were not limited to, the following: (1) To experiment; (2) To feel good or get high; (3) To have a good time with my friends; (4) To increase the effects of some other drugs; and (5) To relieve physical pain.

Substance use disorder (SUD) symptoms at age 35 were measured with several questions based on the DSM criteria for AUD, CUD, and ODUD. Although these measures of SUD symptoms do not yield a clinical diagnosis, the items we used are consistent with the way SUD has been measured in other large-scale surveys (Harford and Muthén, 2001; Muthén, 1996; Nelson et al., 1998) and reflects DSM-IV and DSM-5 AUD and CUD symptoms (Merline et al., 2008; Patrick et al., 2011; Schulenberg et al., 2016). Respondents were asked to report SUD symptoms over the past five years related to AUD, CUD, and ODUD. Fifteen items were used to develop eight of the eleven DSM-5 criteria that were consistent with AUD, CUD, and ODUD: (1) Substance use resulting in a failure to fulfill major role obligations; (2) Continued substance use when physically hazardous; (3) Continued substance use despite persistent or recurrent interpersonal or social problems; (4) Tolerance; (5) Withdrawal; (6) Persistent desire or unsuccessful efforts to cut down substance use; (7) Health-related issue(s) due to substance use; and (8) Craving. The criteria were summed to obtain an overall number of criterion endorsed. We followed recommended practice that any use disorder (including mild, moderate, or severe) was indicated by meeting two or more of the criteria resulting in estimates closely resembling other national estimates for similar age groups (American Psychiatric Association, 2013; Compton et al., 2007; Grant et al., 2015, 2016; Hasin et al., 2007, 2016).

2.3. Data analysis

The analyses included both descriptive statistics and multivariable logistic regression to examine SUD symptoms at age 35 as a function of characteristics associated with NMUPO in adolescence. Descriptive analyses are presented concerning the prevalence of two or more SUD symptoms at age 35 based on eight DSM-5 criteria for AUD, CUD, ODUD, and any SUD as a function of adolescent NMUPO characteristics. Multivariable logistic regression analyses provided adjusted odds ratios (AOR) and 95% confidence intervals (CI) for two or more SUD symptoms at age 35 as a function of characteristics associated with NMUPO during adolescence, controlling for respondent's sex, race/ethnicity, U.S. Census geographic location, urbanicity based on metropolitan statistical area, parental education, annual alcohol use, annual marijuana use, annual other drug use, and baseline cohort year. All the respondents were included in the analyses when possible. Sample sizes varied across analyses due to responses with missing items. All analyses were conducted using STATA 13.1 (Stata Corp, College Station, Texas) and were weighted to adjust for differential attrition at age 35 (see Schulenberg et al., 2016 for more details regarding attrition weights).

3. Results

3.1. Unadjusted associations with future substance use disorder symptoms at age 35

The prevalence of two or more SUD symptoms (i.e., AUD, CUD, ODUD, and any SUD symptoms) at age 35 as a function of NMUPO motives, co-ingestion, prescription opioid schedule and count during adolescence (age 18) were examined (see Table 2). Adolescents who reported NMUPO for pain relief and those who reported NMUPO for only non-pain relief motives had the highest prevalence rates of AUD, CUD, ODUD, and any SUD symptoms at age 35. Nearly half of adolescents who reported NMUPO for pain relief and adolescents who reported NMUPO for only non-pain relief motives reported two or more SUD symptoms at age 35 (48.0% and 52.6%, respectively).

Among adolescents who engaged in past-year NMUPO, approximately 95% also used other substances and the majority simultaneously co-ingested prescription opioids with other substances (55.2%). Adolescents who reported simultaneous co-ingestion involving NMUPO and at least one other substance had the highest prevalence rates of SUD symptoms at age 35 (see Table 2). For instance, most adolescents who engaged in simultaneous co-ingestion of NMUPO with other substances reported SUD symptoms at age 35 (52.0%).

Adolescents who reported any past-year NMUPO involving a Schedule II prescription opioid had the highest prevalence rates of AUD, CUD, ODUD, and any SUD symptoms at age 35. The results also show that any past-year NMUPO involving two or more prescription opioids had the highest prevalence rates of AUD, CUD, ODUD, and any SUD symptoms at age 35.

Table 3 shows the unadjusted prevalence of SUD symptoms at age 35 as a function of lifetime NMUPO frequency during adolescence. The majority of adolescents who engaged in occasional (3–9 times) NMUPO (52.4%) or frequent (10 or more times) NMUPO (52.3%) reported SUD

Table 2
Prevalence of nonmedical use of prescription opioids (NMUPO) and substance use disorder (SUD) symptoms at age 35 as a function of past-year motives, co-ingestion, and specific opioids associated with NMUPO at age 18.

Baseline past-year characteristics (modal age 18)	Alcohol use disorder (AUD) symptoms at age 35 (2+ symptoms) %	Cannabis use disorder (CUD) symptoms at age 35 (2+ symptoms) %	Other drug use disorder (ODUD) symptoms at age 35 (2+ symptoms) %	Any substance use disorder (SUD) symptoms at age 35 (2+ symptoms) %
Past-year NMUPO motives				
No past-year nonmedical use (n = 7574)[b]	26.0	5.5	3.4	27.8
Pain relief (n = 109)	46.7	14.7	15.8	48.0
Non-pain relief (n = 126)	40.3	16.7	20.9	52.6
	(n = 7591)[a]	(n = 7732)[a]	(n = 7330)[a]	(n = 7119)[a]
Past-year NMUPO and co-ingestion				
No past-year nonmedical use (n = 7574)[b]	26.0	5.5	3.4	27.8
No simultaneous co-ingestion (n = 110)	34.3	12.7	11.5	37.5
Co-ingestion with other drugs (n = 136)	43.7	18.4	17.6	52.0
	(n = 7603)[a]	(n = 7743)[a]	(n = 7343)[a]	(n = 7132)[a]
Past-year NMUPO by drug schedules[c]				
No past-year nonmedical use (n = 7598)[b]	26.3	5.6	3.4	28.1
Schedule III, IV, or other only (n = 102)	38.4	13.9	15.2	42.4
Any Schedule II (n = 148)	44.5	18.2	21.2	55.1
	(n = 7633)[a]	(n = 7770)[a]	(n = 7365)[a]	(n = 7158)[a]
Past-year NMUPO: opioid count				
No past-year nonmedical use (n = 7598)[a]	26.3	5.6	3.4	28.1
One opioid (n = 118)	39.3	16.1	11.7	44.5
Two or more opioids (n = 131)	44.5	16.7	25.8	55.1
	(n = 7633)[a]	(n = 7770)[a]	(n = 7365)[a]	(n = 7158)[a]

[a] Sample sizes vary due to missing data on the outcome measures (i.e., AUD, CUD, ODUD, and any SUD symptoms at age 35).
[b] Sample sizes vary due to past-year nonmedical opioid users not selecting any of the ten options for types of prescription opioids used.
[c] Controlled Substances Act Schedule II (e.g., methadone, Demerol, morphine, opium, laudanum and Controlled Substances Act Schedule III, IV and V (e.g., codeine, talwin, paregoric).

Table 3
Prevalence of substance use disorder (SUD) symptoms in early midlife (age 35) as a function of lifetime frequency and medical use history associated with nonmedical use of prescription opioids (NMUPO) during adolescence (age 18).

Baseline lifetime characteristics (modal age 18)	Alcohol use disorder (AUD) symptoms at age 35 (2+ symptoms) %	Cannabis use disorder (CUD) symptoms at age 35 (2+ symptoms) %	Other drug use disorder (ODUD) symptoms at age 35 (2+ symptoms) %	Any substance use disorder (SUD) symptoms at age 35 (2+ symptoms) %
Lifetime NMUPO frequency				
No lifetime nonmedical use (n = 7249)	25.7	5.5	3.2	27.3
Experimental use (1-2 times) (n = 376)	30.5	5.9	7.3	34.5
Occasional use (3-9 times) (n = 209)	45.3	15.0	14.6	52.4
Frequent use (10 or more times) (n = 119)	44.0	13.4	17.9	52.3
	(n = 7733)[a]	(n = 7875)[a]	(n = 7472)[a]	(n = 7272)[a]
Lifetime medical use and NMUPO				
No medical or nonmedical use (n = 6167)	25.4	5.5	3.0	26.9
Medical use only (n = 976)	27.9	6.0	4.3	30.3
Medical before nonmedical use (n = 334)	30.1	4.5	4.8	31.8
Medical after nonmedical use (n = 112)	39.1	16.1	23.1	49.5
Nonmedical use only (n = 259)	45.1	14.0	13.9	53.3
	(n = 7633)[a]	(n = 7770)[a]	(n = 7365)[a]	(n = 7158)[a]

[a] Sample sizes vary due to missing data on the outcome measures (i.e., AUD, CUD, ODUD, and any SUD symptoms at age 35).

symptoms at age 35.

Adolescents who reported the medical use of prescription opioids after initiating NMUPO or who reported only NMUPO had the highest prevalence rates of SUD symptoms at age 35 (see Table 3). Approximately one-half of adolescents who reported the medical use of prescription opioids after initiating NMUPO (49.5%) or only NMUPO (53.3%) during adolescence had SUD symptoms at age 35.

3.2. Adjusted associations with future substance use disorder symptoms

We conducted multivariable logistic regressions to more rigorously consider these associations within adjusted models. Adolescents who indicated NMUPO for pain relief or non-pain relief motives had significantly greater odds of developing AUD, CUD, OUD, and any SUD symptoms at age 35 than adolescents who had no history of NMUPO (see Table 4).

We found that adolescents who engaged in simultaneous co-ingestion of NMUPO and other drugs had significantly greater odds of AUD, CUD, ODUD and any SUD symptoms at age 35 relative to those who had no history of NMUPO during adolescence (see Table 4). In addition, adolescents who reported past-year NMUPO without simultaneous co-ingestion with other drugs had greater odds of reporting subsequent CUD and ODUD symptoms at age 35 relative to those who had no history of NMUPO during adolescence.

Adolescents who engaged in past-year NMUPO involving Schedule II opioids had the highest odds of AUD, ODUD, and any SUD symptoms at age 35 compared to adolescents not engaged in past-year NMUPO. Additionally, adolescents who engaged in past-year NMUPO involving two or more prescription opioids had the highest odds of AUD, CUD, ODUD, and any SUD symptoms at age 35 relative to adolescents not engaged in past-year NMUPO.

Adolescents who reported occasional or frequent NMUPO had significantly higher odds than adolescents with no history of NMUPO of indicating two or more AUD, CUD, ODUD and any SUD symptoms at age 35 (see Table 5). In addition, adolescents who reported experimental NMUPO had significantly higher odds than adolescents with no history of NMUPO of indicating two or more ODUD symptoms at age 35.

Adolescents who indicated medical use without a history of NMUPO did not differ from adolescents with no history of medical use of prescription opioids or NMUPO in the odds of AUD, CUD, ODUD, and any SUD symptoms (see Table 5). In contrast, adolescents who indicated only NMUPO or medical use of prescription opioids after initiating NMUPO (but not before), had significantly higher odds of AUD, CUD, ODUD, and any SUD symptoms at age 35 relative to adolescents who had no history of medical use of prescription opioids or NMUPO.

Additional logistic regression analyses were conducted and we found that adolescents who reported the medical use of prescription opioids after initiating NMUPO had significantly higher odds of CUD symptoms (AOR = 4.06; 95% CI = 1.72, 9.58; $p < 0.001$), ODUD symptoms (AOR = 4.75; 95% CI = 2.02, 11.2; $p < 0.001$), and any SUD symptoms (AOR = 1.98; 95% CI = 1.11, 3.53; $p < 0.05$) at age 35, relative to adolescents who reported the medical use of prescription opioids before initiating NMUPO. Additional analyses also showed that adolescents who reported only NMUPO or medical use after NMUPO had significantly higher odds of AUD, CUD, ODUD, and any SUD symptoms at age 35, relative to those with only medical use of prescription opioids during adolescence. Finally, we examined all the above-mentioned analyses separately by sex and found highly consistent results for adolescent males and females (results not shown).

Additional analyses were conducted to assess whether interaction effects between the main independent variables (e.g., NMUPO motives, co-ingestion, and frequency) and cohort years (i.e., 1976–1980; 1981–1985; 1986–1990; 1991–1996) were associated with AUD, CUD, ODUD, and any SUD symptoms. In general, no consistent interaction effects were found with respect to cohort years. Additionally, we ran

Table 4
Adjusted odds of substance use disorder (SUD) symptoms in early midlife (age 35) as a function of past-year motives, co-ingestion, and specific opioids associated with nonmedical use of prescription opioids (NMUPO) during adolescence.

Baseline characteristics (modal age 18)	Alcohol use disorder (AUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]	Cannabis use disorder (CUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]	Other drug use disorder (ODUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]	Any substance use disorder (SUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]
Past-year NMUPO motives				
No past-year nonmedical use	Reference	Reference	Reference	Reference
Pain relief (n = 109)	2.27 (1.41, 3.66)***	2.83 (1.29, 6.18)**	4.38 (2.04, 9.39)***	2.19 (1.34, 3.58)**
Non-pain relief (n = 126)	1.61 (1.02, 2.52)* (n = 7591)[b]	3.00 (1.81, 4.96)*** (n = 7732)[b]	6.25 (3.37, 11.5)*** (n = 7330)[b]	2.54 (1.57, 4.10)*** (n = 7119)[b]
Past-year NMUPO and co-ingestion				
No past-year nonmedical use	Reference	Reference	Reference	Reference
No simultaneous co-ingestion	1.30 (0.742, 2.29)	2.43 (1.01, 5.85)*	2.97 (1.13, 7.80)*	1.43 (0.807, 2.54)
Co-ingestion with other drugs	1.78 (1.24, 2.55)** (n = 7603)[b]	3.14 (2.02, 4.87)*** (n = 7743)[b]	4.50 (2.80, 7.21)*** (n = 7343)[b]	2.24 (1.54, 3.27)*** (n = 7132)[b]
Past-year NMUPO by drug schedules[c]				
No past-year nonmedical use	Reference	Reference	Reference	Reference
Schedule III, IV, or other only	1.64 (.986, 2.75)	2.85 (1.19, 6.79)*	4.13 (1.69, 10.1)**	1.81 (1.07, 3.09)*
Any Schedule II (n = 148)	1.78 (1.21, 2.61)** (n = 7633)[b]	3.00 (1.96, 4.59)*** (n = 7770)[b]	6.07 (3.63, 10.2)*** (n = 7365)[b]	2.54 (1.69, 3.81)*** (n = 7158)[b]
Past-year nonmedical opioid count				
No past-year nonmedical use	Reference	Reference	Reference	Reference
One opioid	1.56 (1.00, 2.45)*	2.96 (1.46, 5.98)**	2.85 (1.12, 7.25)*	1.80 (1.13, 2.86)*
Two or more opioids	1.88 (1.23, 2.87)** (n = 7633)[b]	2.93 (1.86, 4.64)*** (n = 7770)[b]	7.96 (4.69, 13.5)*** (n = 7365)[b]	2.69 (1.74, 4.19)*** (n = 7158)[b]

$p < 0.05$*, $p < 0.01$**, $p < 0.001$***.

[a] All analyses control for race/ethnicity (i.e., White, Black, Hispanic, Other race/ethnicity); sex (i.e., Male, Female); highest level of parental education (i.e., At least one parent has a college degree or higher, Neither parent has a college degree); geographic region (i.e., Northeast, Midwest, South, and West); metropolitan statistical area (i.e., Large MSA, Other MSA, Non-MSA); baseline cohort year; and baseline measures of past-year alcohol use, past-year marijuana use, and past-year other drug use.

[b] Sample sizes vary due to missing data on the outcome measures (i.e., AUD, CUD, ODUD, and any SUD symptoms at age 35).

[c] Controlled Substances Act Schedule II (e.g., methadone, Demerol, morphine, opium, laudanum and Controlled Substances Act Schedule III, IV and V (e.g., codeine, talwin, paregoric).

Table 5
Adjusted odds of nonmedical use of prescription opioids (NMUPO) and substance use disorder (SUD) symptoms in early midlife (age 35) as a function of lifetime frequency and medical use history associated with NMUPO during adolescence.

Baseline characteristics (modal age 18)	Alcohol use disorder (AUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]	Cannabis use disorder (CUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]	Other drug use disorder (ODUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]	Any substance use disorder (SUD) symptoms at age 35 (2+ symptoms) AOR (95% CI)[a]
Lifetime NMUPO frequency				
No lifetime nonmedical use	Reference	Reference	Reference	Reference
Experimental use (1-2 times)	1.17 (0.855, 1.61)	1.02 (0.605, 1.74)	2.08 (1.24, 3.49)**	1.28 (0.928, 1.77)
Occasional use (3-9 times)	1.98 (1.38, 2.85)***	2.67 (1.57, 4.53)***	4.24 (2.38, 7.53)***	2.45 (1.68, 3.57)***
Frequent use (10 or more times) (n = 119)	1.95 (1.18, 3.23)** (n = 7733)[b]	2.27 (1.28, 4.05)** (n = 7875)[b]	5.89 (2.93, 11.8)*** (n = 7472)[b]	2.47 (1.46, 4.18)*** (n = 7272)[b]
Lifetime medical use and NMUPO				
No medical or nonmedical use	Reference	Reference	Reference	Reference
Medical use only	1.06 (0.852, 1.33)	1.11 (0.712, 1.72)	1.31 (0.758, 2.25)	1.12 (0.895, 1.39)
Medical use before nonmedical use	1.19 (0.834, 1.70)	0.796 (0.463, 1.37)	1.52 (0.777, 2.97)	1.18 (0.821, 1.72)
Medical use after nonmedical use	1.62 (1.02, 2.56)*	3.24 (1.58, 6.62)***	7.22 (3.75, 13.9)***	2.35 (1.46, 3.77)***
Nonmedical use only	1.95 (1.39, 2.74)*** (n = 7633)[b]	2.27 (1.44, 3.58)*** (n = 7770)[b]	4.29 (2.57, 7.18)*** (n = 7365)[b]	2.47 (1.74, 3.52)*** (n = 7158)[b]

$p < 0.05$*, $p < 0.01$**, $p < 0.001$***.

[a] All analyses control for race/ethnicity (i.e., White, Black, Hispanic, Other race/ethnicity); sex (i.e., Male, Female); highest level of parental education (i.e., At least one parent has a college degree or higher, Neither parent has a college degree); geographic region (i.e., Northeast, Midwest, South, and West); metropolitan statistical area (i.e., Large MSA, Other MSA, Non-MSA); baseline cohort year; and baseline measures of past-year alcohol use, past-year marijuana use, and past-year other drug use.

[b] Sample sizes vary due to missing data on the outcome measures (i.e., AUD, CUD, ODUD, and any SUD symptoms at age 35).

interaction effects between prescription opioid use at age 18 and several demographics (i.e., sex, race, and cohort year) to assess how these interaction effects were associated with AUD, CUD, ODUD, and any SUD. None of these interaction effects reached statistical significance.

4. Discussion

This is the first prospective national study in the U.S. to identify a distinct sequence of initiation of medical use of prescription opioids and NMUPO (i.e., medical use after initiating NMUPO) during adolescence that was associated with increased risk for future SUD symptoms at age 35. Nearly one in every two adolescents who reported the medical use of prescription opioids after initiating NMUPO had two or more SUD symptoms at age 35. These results indicate substantial risk for developing SUD among adolescents who have already initiated NMUPO and reinforce the critical role of screening when prescribing opioid analgesics to adolescents. Screening for a history of NMUPO should be conducted in a non-judgmental manner to detect high-risk adolescents for indicated interventions to reduce prescription opioid misuse and SUDs.

The present study is the first prospective national investigation to identify adolescent characteristics associated with NMUPO (i.e., frequency, misuse potential, motives, and co-ingestion) that is significantly associated with future SUD symptoms in adulthood. While past research has clearly established an increased risk of substance use behaviors and SUDs among adolescents and young adults who engage in NMUPO based on cross-sectional and longitudinal findings (Boyd et al., 2009; Han et al., 2015; McCabe et al., 2007a, 2009, 2013, 2016; Muhuri et al., 2013; Saha et al., 2016), the present study adds to the existing knowledge by showing that occasional or frequent NMUPO, pain relief and non-pain relief motives, simultaneous co-ingestion, opioids with high misuse potential (e.g., Schedule II), and multiple prescription opioids during adolescence *significantly predicts* subsequent SUD symptoms nearly two decades later at age 35. This new information indicates youth substance use assessment instruments may consider including these NMUPO characteristics to help detect high-risk adolescents.

4.1. Findings

The present study found that 95% of past-year NMUPO involved concurrent or simultaneous polysubstance use, and the majority of NMUPO involved simultaneous co-ingestion of prescription opioids and other substances. The findings indicated that simultaneous co-ingestion involving NMUPO and other substances during adolescence is highly prevalent and a strong signal for future SUD symptoms in adulthood. Furthermore, adolescents engaged in NMUPO are more likely to develop AUD symptoms than other SUD symptoms at age 35 (even after controlling for baseline alcohol and other drug use). Taken together, these findings indicate the importance of health professionals viewing NMUPO within a wide range of substance use to account for the high rates of polysubstance use associated with NMUPO among adolescents and young adults shown in the present study and prior work (Catalano et al., 2011; McCabe et al., 2006, 2012).

A substantial proportion of adolescents who engaged in NMUPO were motivated by physical pain relief consistent with prior studies (Boyd et al., 2006; McCabe et al., 2007b; Young et al., 2012b). The present study found that nearly half of adolescents who reported NMUPO for physical pain relief had two or more SUD symptoms at age 35. Furthermore, the majority of adolescents who reported occasional NMUPO (i.e., 3–9 occasions) had two or more SUD symptoms at age 35. Thus, it is important for health professionals to recognize the increased risk for developing SUD symptoms associated with NMUPO for self-treating pain and infrequent NMUPO. These findings suggest screening and brief interventions should incorporate frequency and motives for NMUPO to help identify youth who engage in NMUPO and may require more comprehensive pain management and SUD assessments.

4.2. Strengths

Strengths of this study include the following. First, this study includes multiple cohorts of nationally representative samples of high school seniors in the U.S with consistent measurement and methodology over time. Second, the high school seniors were followed longitudinally over 17 years, enabling the prospective association between adolescent NMUPO and subsequent SUDs. To date, most national studies have been cross-sectional and have not examined distinct characteristics of NMUPO and temporal patterns of medical use and NMUPO during adolescence or followed adolescents into adulthood.

4.3. Limitations

This study also has the limitations associated with prospective survey research using self-administered surveys. All measures were subject to the potential response bias introduced when assessing sensitive behaviors via self-report surveys administered in a school setting. The MTF study attempted to minimize these biases by informing potential respondents that participation was voluntary and assuring potential respondents that data would remain confidential (Harrison and Hughes, 1997; O'Malley et al., 1983). In addition, the study does not include some variables at baseline that are likely related to adult SUD symptoms (e.g., family history of SUD). Finally, findings from U.S. secondary school students do not necessarily apply to the general U.S. population or other countries but require replication with different subpopulations in the U.S. and further investigation in other countries.

In conclusion, the findings of the present study fill important knowledge gaps regarding long-term associations between adolescent exposure to prescription opioids and subsequent SUDs in adulthood. We identified several characteristics associated with NMUPO that should be carefully assessed to detect high-risk individuals for future adult SUDs. This finding leads us to conclude that health professionals who prescribe opioids to adolescents should carefully screen all patients for prior or present NMUPO or other substance misuses to detect those at risk for SUDs. Clinicians should educate patients, particularly parents/guardians of adolescents, about proper opioid analgesic monitoring, safe storage, and innovative disposal options to limit the amount of leftover opioid medication via controlled medication contracts. Given the risk for substance-related problems associated with even occasional opioid misuse by adolescents, such proactive efforts are warranted. Finally, prescribers who detect adolescent patients with a history of NMUPO should consider referring these youths for more comprehensive substance use assessment.

From a public policy perspective, healthcare assessment and interventions need to be tailored to at-risk populations as opposed to blanket statements and policies around drug classes such as opioids that may have unintended consequences. Use of clinical decision support systems, through electronic health records, could promote more precise and judicious opioid prescribing, ultimately promoting value-based care. Accordingly, policymakers need to continue to promote measures to adequately treat pain while limiting the amount of leftover opioid medications by encouraging appropriate education, prescribing, monitoring and disposal of opioid medications.

5. Contributors

Dr. S.E. McCabe designed the study. Drs. S.E. McCabe, T.S. Schepis and V.V. McCabe managed the literature searches and summaries of previous related work. Dr. J.E. Schulenberg helped design the surveys and oversee the collection of the data. Dr. P. Veliz undertook the statistical analysis. Dr. S.E. McCabe wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict declared.

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